The Relationship Between Blood Pressure and Pain

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The relationship between pain and hypertension is potentially of great pathophysiological and clinical interest, but is poorly understood. The perception of acute pain initially plays an adaptive role, which results in the prevention of tissue damage. The consequence of ascending nociception is the recruitment of segmental spinal reflexes through the physiological neuronal connections. In proportion to the magnitude and duration of the stimulus, these spinal reflexes cause the activation of the sympathetic nervous system, which increases peripheral resistances, heart rate, and stroke volume. The response also involves the neuroendocrine system, and, in particular, the hypothalamic-pituitary-adrenal axis, in addition to further activation of the sympathetic system by adrenal glands. However, in proportion to an elevation in resting blood pressure, there is a contemporary and progressive reduction in sensitivity to acute pain, which could result in a tendency to restore arousal levels in the presence of painful stimuli. The pathophysiological pattern is significantly different in the setting of chronic pain, in which the adaptive relationship between blood pressure and pain sensitivity is substantially reversed. The connection between acute or chronic pain and cardiovascular changes is supported observationally, but some of this indirect evidence is confirmed by experimental models and human studies. The pain regulatory process and functional interaction between cardiovascular and pain regulatory systems are briefly reviewed. Various data obtained are described, together with their potential clinical implications. *J Clin Hypertens (Greenwich).* 2013;15:600–605. ©2013 Wiley Periodicals, Inc.

In healthy individuals, functional interactions exist between the cardiovascular and pain regulatory systems. These relations are profoundly different in acute vs chronic pain.

While it is widely recognized that pain can raise blood pressure (BP) acutely, the evidence that hypertension is associated with a reduced sensitivity to acute pain is less known.[1] Therefore, in the setting of acute pain, an inverse relationship between resting BP levels and pain sensitivity defines a clinical feature called "hypertension-associated hypoalgesia." This condition is believed to reflect homeostatic feedback that helps to restore arousal levels in the presence of acutely painful stimuli.[2]

On the other hand, the relationship between hypertension and chronic pain is still a matter of debate.[3] Overall, the complex alterations of the entire nociceptive system failure are regarded as the result of a maladaptive process.

This review summarizes the available information about the possible pathophysiological mechanisms underlying these two different conditions, and suggests their potential clinical implications.

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ACUTE PAIN AND BP RESPONSE

Adaptation to Acute Pain: General Concepts

The ability to adapt to an acute pain stimulus is an important contributor to quality of life. Acute pain is considered a warning alarm to prevent danger and to maximize survival. Adaptation to pain is the result of a complex endogenous pain regulatory network made of both descending inhibitory and descending facilitatory pathways.[4]

The initial response to nociceptive stimuli is the activation of some components of the peripheral and central nervous system (Figure 1). In addition, substances such as adrenocorticotropic hormone, β-endorphin, and prolactine are released from the anterior pituitary gland, glucocorticoids from the adrenal cortex, epinephrine from the adrenal medulla, and norepinephrine from the sympathetic nerves. Reactions to stressors typically involve either short- or long-term compensatory changes in cardiovascular, endocrine, immune, and somatosensory systems, which tend to maintain adequate physiological function against the imbalance created by the stressors (Figure 2).[4]

In nature, acute pain signals by tissue trauma and sensitization inhibits normal behavior in a protective manner to minimize risk and promote tissue healing. Although unpleasant, acute pain promotes survival.

Some descending pathways contribute to the modulation of pain transmission at the spinal level, through a postsynaptic action on the projections of neurons or on interneurons of the dorsal horn. Direct connections

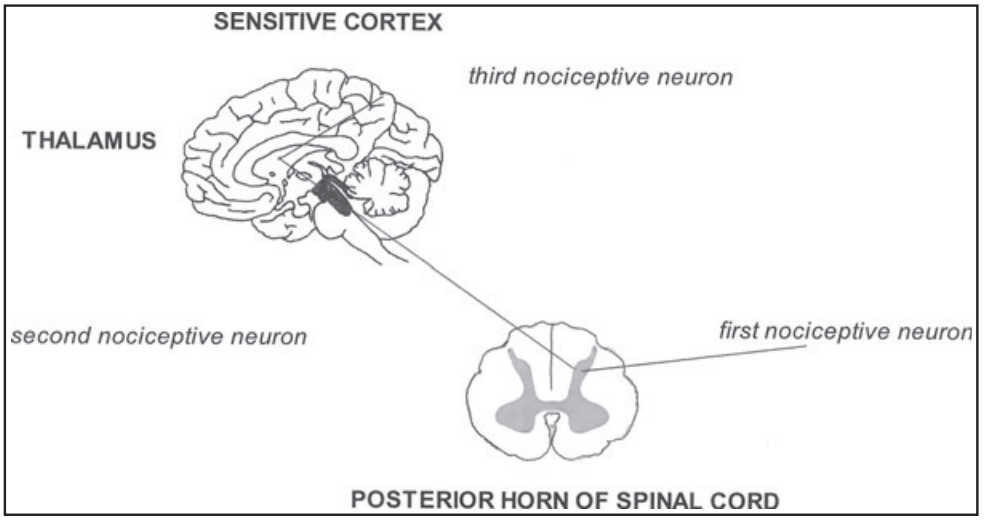

FIGURE 1. The detection of noxious stimuli requires the activation of peripheral sensory organs and the signal transduction pathways for the conduction to the central nervous system. The transport of the nociceptive information to the higher levels of the central nervous system occurs through multiple and parallel upward projections, which lead the signal from the spinal cord to the centers of the prosencephalon, mesencephalon, and cortex.

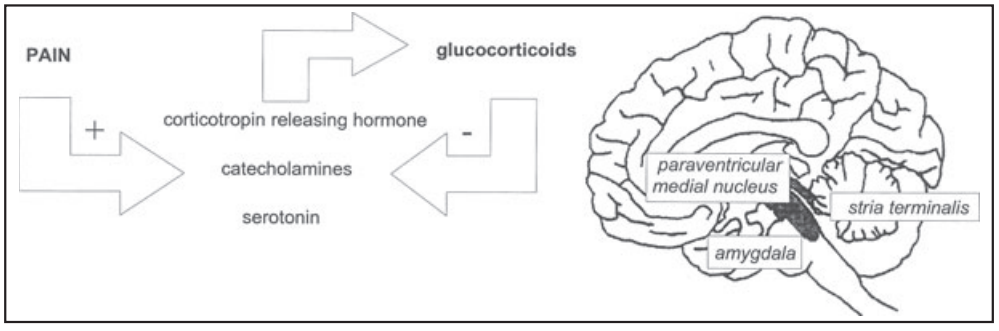

FIGURE 2. The beginning of the pain reaction, elicited by nociceptive stimuli, mainly activates norepinephrine- and corticotropin-releasing hormone by locus coeruleus. The adaptability of the body to environmental changes is specifically modulated in various brain areas by different circuits. The central amygdaloideus nucleus, receiving enteroceptive pathways, is indirectly linked to the brainstem, while the medial one, activated by emotional stimuli, is synaptically linked to the paraventricular medial nucleus by the stria terminalis, the preoptic area, and the anterior hypothalamus. Serotonin and acetylcoline stimulates hypothalamus-pituitary-adrenal axis, while nitric oxide and gamma-aminobutyric acid inhibit corticotrophin and vasopressin release, trough limbic system. Catecholamines and serotonin release are regulated by the levels of cortisol, determining the phenomena of habituation to repeated or new pain stresses.

departing from the cortex or indirect ways involving the hypothalamus and brainstem are part of this system. The system of nerve pathways, transmitters, and receptors that constitute the descending modulation can determine two opposing effects on pain transmission, namely facilitation (excitatory effect) or inhibition.[5] Often, this system can also lead to behavioral consequences. Specifically, a painful stimulus starts the descending inhibitory pathway that allows the organism to escape from an injury-causing event, without experiencing feelings of intense pain that may interfere with the immediate survival. When the acute danger has passed, the pain regulatory system shifts to a relative predominance of descending facilitatory pathways that hold on the pain as a signal to prevent injury and allow the healing (ie, protective reflexes of the injured area).[5] According to the International Association for the Study of Pain (IASP), pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[6] From the point of view of neuroanatomy, a descending pathway originates from the locus coeruleus and sends axons to the dorsal horn, where occurs the release of norepinephrine, which inhibits substance P and reduces the perception of pain. The second descending pathway originates from the periaqueductal gray of mesencephalon and the dorsal raphe nucleus of

the medulla oblongata, projecting the axons to the spinal cord to the release of serotonin[7] (Figure 3).

Acute pain generates an increasing sympathetic nerve activity. Scientists developed many animal models to study this phenomenon. One of the most utilized investigation is to observe directly from electrode, inserted into peroneal nerve, the detection of different sympathetic fibers: those going to the skin, involved in thermoregulation, and those going to the muscle, which are under control of the baroreceptors. The most commonly used painful stimulus is the cold pressor test.[8] This test shows that the production of a remarkable increase in muscle sympathetic nerve activity is associated with a marked increase in BP.[9] The same reaction can be found with other kinds of painful stimuli such as the application of physical pressure to the nail beds or the skin of the cheek or during electrical stimulation of a digital nerve.[8] Another widely used stimulus has been the forearm ischemia produced by a cuff inflated to cut off the blood supply. In this test, the degree of pain correlates with the increase in BP and vascular resistances.[10]

This phenomenon is well explained and understandable by most, but the altered perception of pain in hypertensive rats and humans is not so well known and needs more research to be clarified.

From Animals to Humans: Hypotheses for the Mechanisms of Hypertension-Associated Hypoalgesia

Several studies have reported that acute or chronic hypertension is associated with behavioral hypoalgesia in rats.[2] Ghione and colleagues[11] compared spinal nociceptive transmission in normotensive Wistar–Kyoto rats (WKY) and spontaneously hypertensive rats (SHR). The authors showed the responses to noxious heating of the hind foot of varying intensity (temperature) for two types of dorsal horn neurons involved in nociceptive transmission: the wide-dynamic-range (WDR) neurons, which respond also to non-noxious stimuli, and the high-threshold (HT) neurons, which respond only to noxious stimuli. For both WDR and HT neurons, a rightward shift of the response curve in relation to the intensity of the noxious stimulus was observed in SHR compared with WKY. That is to say that the responses of both types of neurons appear to be more delayed and less intense in SHR than WKY.[11] Other varieties of animal models of experimental hypertension are the Goldblatt hypertension model (clipping a renal artery of a rat induced hypoalgesia as well as hypertension)[11] and the deoxycorticosterone acetate–salt hypertension or Dahl salt-sensitive rats on a high-salt diet.[12]

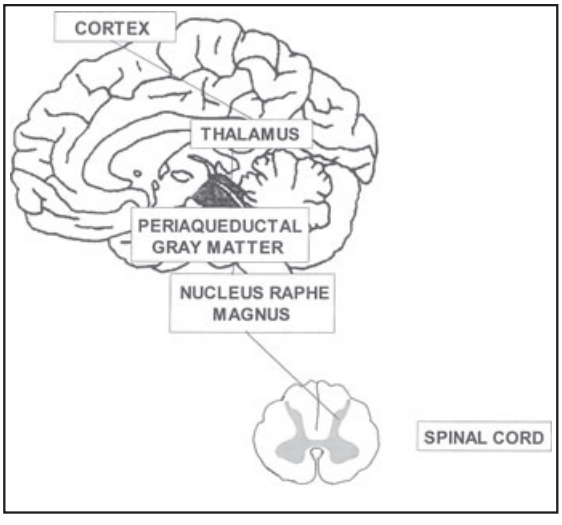

FIGURE 3. Neuroanatomy of the descending pathway.

In humans, different painful stimuli have been studied, such as tooth pulp, electrical stimulation, and thermal stimulation.[13] All studies confirmed the same association of the rat model reaction, finding the same hypertension-associated hypoalgesia. In other words, BP correlates positively with the pain threshold and negatively with the perception of the intensity of the painful stimulus in acute pain models.[14] Moreover, the association between pain sensitivity and BP holds even within the normal range of BP,[11] and some studies have suggested that hypoalgesia may precede hypertension in normotensive persons with a family history of hypertension.[15] Finally, it has been confirmed that pain tolerance measured at age 14 may predict ambulatory BP at age 22.[16]

At this point, investigators should ask themselves the classic "chicken and egg" question: is the hypoalgesia secondary to hypertension or does it contribute to the genesis of hypertension? Some evidence would seem to show that hypoalgesia in hypertensive rats is present at a young age, even before they develop hypertension. On the other hand, hypoalgesia is not observed in all rats that have undergone the clipping of the renal artery in experimental models. Finally, the administration of antihypertensive drugs has never demonstrated a significant reduction of hypoalgesia.[5]

At the moment we only know that the increase in pain threshold and reduced perception of painful stimuli may be mediated by an increase in the inhibitory descending pathways, and that this central activity may be associated with the development of arterial hypertension.[5] Moreover, resting BP is inversely correlated with acute pain sensitivity in healthy normotensive patients, and presurgical resting systolic BP is inversely associated with acute postsurgical pain intensity.[17] These observations can be transposed to clinical practice. It is not yet entirely clear whether an exaggerated hypoalgesia may be associated with a real risk of developing high BP, or whether it should be considered only a predictive, pathophysiological marker of predisposition. Conversely, the relationship between BP and pain sensibility in normotensive patients can be read as an adaptive, homeostatic feedback that helps to re-stabilize the system in the presence of acute pain.

In the autonomic nervous system network of the brain, some regions are described to coordinate integrated responses to environmental stimuli. The regions that control the cardiovascular system largely join those that contribute to the antinociception.[18]

In particular, the nucleus of the solitary tract represents an interface between autonomic nervous system and sensory system: it is the first synapse station in the pathway of the baroreceptor reflex. The nucleus of the solitary tract is also an important link with both the vagus nerve and the dorsal laminae of the spinal cord.[18] The pain activates the sympathetic nervous system with resulting increase in BP, which, in turn, causes increased stimulation of baroreceptors that consecutively activate the descending inhibitory pathways of pain, restoring initial homeostasis (Figure 4). For example, it is observed that an acute rise of BP may reduce reactivity to noxious stimuli through a baroreceptor-mediated reduction of cerebral arousal in experimental rats. When BP was raised by an infusion of phenylephrine, rats showed less running to terminate or avoid noxious stimuli than during saline infusions.[2] This effect was not seen in rats with denervated baroreceptors.[2]

Among other mechanisms that may be responsible for hypertension-associated hypoalgesia, in addition to the overlap between the anatomical nervous systems involved, the opioid and noradrenergic transmission systems can play a role. The role of the endogenous opioid system in the expression of the relationship between BP and pain is well known in animal models. It has been shown that the reduced pain sensitivity in rats with hypertension is pharmacologically reversible as a result of the inhibition of the MOR opioid receptor,[19] but studies in humans have reported controversial results.[20] These showed that the relationship between BP and pain may occur in normotensive patients even in the absence of an opioid system–working action, and the blocking of the opioid receptor with the antagonist (naloxone) did not work in reversing pain sensitivity.[20] In the noradrenergic system, the α_2 receptors are critical components of the descending inhibitory pain pathways. There are numerous interconnections for the regulation of the cardiovascular system and the inhibitory descending pathways of the pain system, which have a large population of noradrenergic fibers and receptors with an impact on both systems.[18] For example, the nucleus of the raphe magnum is activated by nociceptive stimulation. It activates the excitatory pathways of neurotransmitters that increase the release of norepinephrine from the locus coeruleus by activating the descending noradrenergic pathway, which leads to anti-nociception through the activation of α_2 spinal receptors.[18]

Several conceptual problems still exist. The data derived from animal studies are based on models of very defined experimental hypertension, as shown for example in SHR or Goldblatt rats. Instead, human hypertension is a multifactorial disease, in which it is very difficult to distinguish the endocrine neurological and genetically determined components.[21] For the same reason, the possibility of hypoalgesia in individuals with a family history of hypertension remains to be epidemiologic but not causal evidence at present.[21] Sex differences in pain responses to the cold pressor test in persons with a positive or negative parental history for hypertension were investigated with the same result.[22] In the same way, in everyday practice, we cannot correlate the data of hypoalgesia and high BP with prognostic significance or routine clinical use.[22]

CHRONIC PAIN AND HYPERTENSION

While the above-reported pain process has been considered as adaptive, the development of chronic pain is clearly maladaptive. In chronic pain, the relationship between hypertension and pain sensitivity is completely reversed.

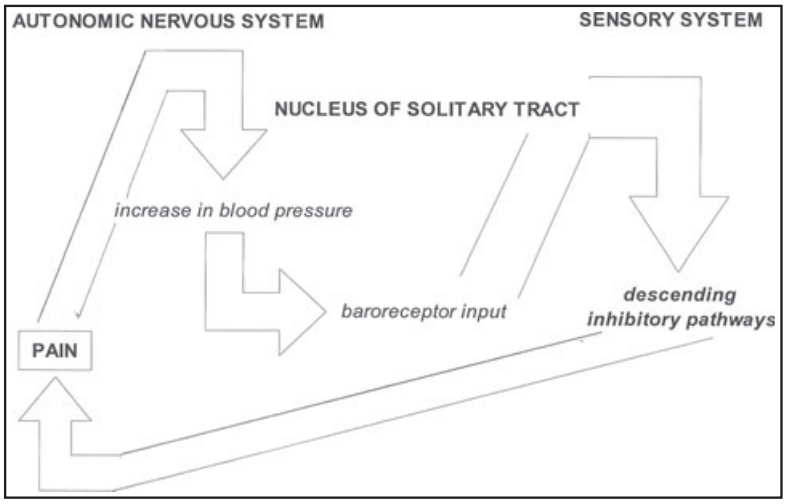

FIGURE 4. Mechanisms of interaction between control of the cardiovascular system and nociception.

In patients with chronic low back or orofacial pain, elevated BP levels at rest were associated with an increased sensitivity to acute pain and a higher intensity of chronic pain.[23]

Some studies suggest that the typical inverse relationship between resting BP and acute pain sensitivity may be altered in chronic pain conditions, with consequences for the experience of clinical pain as well.[24] The observed alterations in the BP-pain sensitivity relationship are likely to reflect wider alterations in endogenous pain regulatory systems related to chronic pain. As previously defined, the pain regulatory system is represented by both pain inhibitory and facilitatory pathways. There is evidence suggesting that activity in both of these pathways is altered in chronic pain conditions. This dysfunction may be related to the sensitivity of baroreceptors, which appears to be decreased in chronic pain. Alternatively, the explanation may lie in an impairment of the descending inhibitory pain pathways normally activated by an increase in the stimulation of baroreceptors.[23] The altered cardiovascular-pain regulatory system interactions in individuals with chronic pain have been found in patients with chronic back pain in response to experimental stimulation of carotid baroreceptors.[25] The group of patients with chronic pain reported greater pain during the activation of baroreceptors compared with controls. In this study, the activation of baroreceptors was measured by the noninvasive mechanical manipulation of baroreceptors with the Phase-Related External Suction technique. Furthermore, the group of patients with chronic pain showed lower diastolic BP. Finally, the study showed an increased sensitivity to electrical pain rather than the diminished pain responsiveness, typically reported in pain-free individuals.

Studying temporo-mandibular joint chronic pain, Maixner and colleagues[23] reported that patients affected by temporo-mandibular disorders (TMDs) are more sensitive to noxious stimuli. They also suggest that painful TMDs may result, at least in part, from an impairment in central pain regulatory systems that are influenced by resting arterial BP.[23] They determined resting arterial BP and measured thermal and ischemic pain threshold and tolerance in TMD patients vs pain-free controls. The pain-free high resting BP subgroup had higher thermal pain tolerances, higher ischemic pain thresholds, and provided lower magnitude estimates of the intensity of graded heat pulses when compared with the pain-free low-BP subgroup. In contrast to the pain-free group, BP level did not influence ischemic or thermal pain perception for TMD patients. Postulating two major pain modulatory mechanisms (the baroreceptor reflex arc and endogenous opioid system), the same authors described the relationship between pain sensitivity and resting arterial BP in patients with painful TMD compared with pain-free women and men.[26] The main results were that a BP-related analgesic mechanism (probably baroreceptor-mediated) predominates in pain-free men, while an endogenous opioid mechanism predominates in pain-free women. Moreover, stress enhances the expression of central mechanisms: indeed, women with TMD appear unable to effectively engage the normal pain inhibitory systems. Finally, MOR desensitization and/or downregulation are probably implicated, because, in the TMD group, the production of β-endorphins appeared normal.[26]

Studies from Bruehl and colleagues[5] have investigated the relationship between hypertension and pain sensitivity in low back pain, probably the most common chronic pain condition in the general population. A positive relationship between resting BP and clinical chronic pain intensity has been observed. They also suggested that the pain regulatory dysfunction reflected in this positive BP-chronic pain relationship is progressive, in relation to the duration of pain (more than 2 years). That condition would be supported by a gradual exhaustion of pain inhibitory systems or gradual changes in baroreceptor function.

HYPERTENSION AND PAIN: POSSIBLE CLINICAL IMPLICATIONS

According to our study, in an effort to find continuum between the pressor response to nociception in acute and chronic conditions, we can assume the following: acute pain causes an increase in baroreceptor stimulation, which abruptly reduces the sensitivity to pain in part due to a transient increase of endogenous opioids. On the contrary, persistent pain tends to become chronic and to increase BP values: after a long time, dysfunction of the release of endogenous opioids results in a reduction of their analgesic effect. In this way a vicious circle is established, where further pain leads to a reduction in pain tolerance associated with decreased analgesia mediated by baroreceptors, in a kind of process of exhaustion.[24]

The first clinical implication in hypertension-associated hypoalgesia that we find in acute pain may be the phenomenon of silent myocardial ischemia and infarcts. Some studies demonstrated that patients with silent ischemia have a higher pain threshold, eg, to tooth pulp testing.[27] Furthermore, silent ischemia seems to be more common in hypertensive patients than in normotensive patients, and, in the Framingham study, unrecognized or silent myocardial infarcts were nearly twice as common in hypertensive patients than in normotensive patients.[28]

Regarding the possible implications of a maladaptive process between chronic pain and hypertension, the reduced function of the baroreceptors could have significant clinical implications, increasing cardiovascular morbidity and the pathogenesis of hypertension. If spontaneous baroreflex sensitivity inhibits wind-up (an index of central pain sensitization) in healthy individuals, in patients with chronic pain the absence or reversal of normal interactions between overlapping systems modulating cardiovascular function and pain may contribute to impaired cardiovascular regulation and increased hypertension and cardiovascular risk.[29]

CONCLUSIONS

A retrospective study has directly examined the question of hypertension as it relates to chronic pain.[3] The results suggest that if the alterations related to chronic pain in the functional interactions between the cardiovascular and pain systems reflect the failure of overlapping systems, it may be possible to have an increased prevalence of hypertension in a chronic pain population. In this study, it was shown that the intensity of chronic pain was a significant predictor of hypertensive status, independent of the effects of age, race, ethnicity, and parental hypertension. These results suggest the possibility that chronic pain may be associated with increased risk of hypertension.

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